

REMARKS

Amendment to the specification on page 4 has been made to remove inconsistencies in the specification. Specifically, in the paragraph beginning at line 6, amendment has been made to identify the channel as demonstrating both a transient and persistent current. This correlates the summary of the invention with the remainder of the specification appearing on pages 1 and 5. Accordingly, no new matter has been added. In addition, claims 1, 3, and 5 have been amended to more clearly define the present invention and overcome the Examiner's rejections as identified hereinbelow.

Turning to the rejections, claims 1-4 have been rejected by the Examiner under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Specifically, the Examiner notes that in claim 1, the phrase "the channel blocker demonstrating both a transient and persistent current", is not clear. Claim 1 has been amended to remove this obvious error in terminology. As pointed out by the Examiner, it is not clear how the channel blocker could have a current period.

In fact, as set forth in the specification, the channel demonstrates both a transient and persistent current. Accordingly, no new matter has been added by the amendment of claim 1 by the removal of a term "blocker".

The Examiner has stated that claim 3 is vague and indefinite with the recitation of the term "very similar". Not to overcome this amendment, the applicant has amended claim 3 to remove the term "very". Support for this amendment is found on page 5 of the original specification on line 20 wherein it is stated, "for optimal sensitivity the K conductants (g_K) and persistent Na^+ conductants ($g_{Na_{persistent}}$) should be similar (order of magnitude)." Accordingly, the specification does provide a standard for ascertaining the requisite degree for the term "similar".

Claim 5 has been rejected by the Examiner under 35 USC 112, second paragraph, as being vague and indefinite through the recitation of the term "screen". The Examiner has stated it is not clear whether the use of this term is meant to note the claim covers an apparatus for carrying another method or whether the claims as directed to a method.

To clarify this confusion, the applicant has amended the claim to define an apparatus for identifying a Na^+ channel blocker. This amendment is supported by the original specification on page 4, last paragraph.

Accordingly, the applicants submit that the present amendment to the claims overcomes the Examiner's rejection of the claims under 35 USC 112, second paragraph. Withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 1-5 under 35 USC 103(a) as being anticipated by W096/41166 to Tsien, et al.

in view of U.S. 5,981,268 to Kovacs, et al. and further in view of Gleitz, et al. (1955).

In this rejection, the Examiner is states that Tsien, et al. teaches method of assaying for small changes in transmembrane potential using voltage sensitive dyes and optically measuring the change in membrane potential.

The Examiner acknowledges that Tsien, et al. does not teach a method using a stimulating current to generate an action potential and accordingly reaches to Kovacs, et al. for disclosing a method wherein a stimulating current is passed to initiate an action potential, referring to column 19, lines 40-44.

This general reference to the use of a stimulating current by Kovacs, et al. in combination with the Tsien, et al. reference does not provide a basis for a prima facie case of obviousness for the present inventive method for identifying Na^+ channel blockers that preferentially block persistent over transient Na^+ channels (claim 1 as amended) (see also page 10, line 7, of the original specification).

Neither the Tsien, et al. or Kovacs reference teach the sequential steps of applying a stimulating current to a cell engineered to contain Na^+ channels capable of producing both the transient and persistent Na^+ currents in order to distinguish channel blockers that preferentially block persistent over transient Na^+ .

The Examiner is utilizing a present application as an instruction manual or "template" pieced together teachings

of the prior art in an effort to render the claimed invention obvious.

While, as an abstract proposition, it might be possible to select certain statements from one reference and mechanically combine them with another reference to arrive at the applicants claimed combination, there is no basis for making such a combination; only the applicants specification suggests any reason for combining the teachings of the prior art. But the use of suggestion is, of course, improper under the mandate of 35 USC 103. In re Pye and Peterson, 148 USPQ 426 (CCPA 1966).

Further, the applicants submit that the combination is improper since the use of electrical stimulating current in the Tsien, et al. reference would destroy the reference for its intended purpose. Tsien utilizes changes in membrane potential to cause the fluorescent N ion to migrate across the membrane so that it can continue to bind to whichever face is positively charged. As set forth in page 4, beginning with line 18, Tsien, et al. states, "Thus, fluorescence measurements at appropriate excitation and emission wavelengths provide a fluorescent read out which is sensitive to the changes in the transmembrane potential."

If a stimulating current were applied to the Tsien, et al. reference, the membrane potential would be changed, thus affecting the migration of the fluorescent ion and producing false readings. Accordingly, the incorporation of the Kovacs, et al. reference into the Tsien, et al. reference would result in an inoperative assay.

Finally, with regard to obviousness, the question is whether what the applicants did would be obvious from the references and combination.

As hereinabove noted, clearly the combination of the Tsien, et al. reference with the Kovacs, et al. reference, in view of its inoperativeness, would not make the present invention obvious.

Accordingly, the Applicants respectfully request to withdraw the rejection on claims 1-5 under 35 USC 103(a) on the basis of the Tsien, et al. and Kovacs references.

With specific reference to claim 4, which includes adding ouabain to the well in order to block the Na^+ pump, the Examiner relies on Gleitz J, as showing the effectiveness of using ouabain to differentiate the effects of the sodium pump. The Examiner concludes it would have been obvious to one of ordinary skill in the art at the time the invention was to practice the method of identifying a Na^+ channel blocker using a voltage sensitive dye, simulating an action potential with an external stimulus electrode in monitoring of the membrane potential using optical means, and differentiating the activity of the voltage gated Na^+ channel for the Na^+ pump using ouabain.

First, the selective application of passing the stimulating current through the cell sufficient to generating action potential before and after the addition of Na^+ channel blocker and optically measuring a change in

the cell membrane potential before and after the passage of a stimulating current in order to identify Na⁺ channel blockers that preferentially block persistent over transient Na^{channels} is not taught or suggested by Gleitz, et al.

Accordingly, the addition of Gleitz, et al. reference to the combination of Tsien, et al. and Kovacs, et al. does not provide a basis for sustaining a prima facie case of obviousness under 35 USC 103(a).

In view of the arguments hereinabove set forth in amendment to the claims, it is submitted that each of the claims now in the application define patentable subject matter not anticipated by the art of record and not obvious to one skilled in this field who is aware of the references of record. Reconsideration and allowance are respectively requested.

Respectfully submitted,



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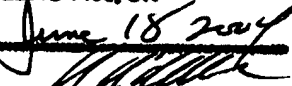

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